Identifying Risk Factors for Anxiety and Depression in Patients with Chronic Lymphocytic Leukemia

Research Thesis

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by

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Abstract

The American Society of Clinical Oncology (ASCO) has provided risk factors (past psychiatric history, gender, low SES, additional chronic illness, and martial status) for greater anxiety (GAD-7) and depressive (PHQ-9) symptom severity in the general cancer population. ASCO and additional cancer-specific (cancer-specific stress, social contacts, social support, life events and age) and CLL-specific (absolute lymphocyte counts, treatment naïve, and fatigue) risk factors were measured in patients with chronic lymphocytic leukemia (CLL) to determine whether the ASCO risk factors were applicable to this more specific cancer population. Patients diagnosed with CLL ($N = 130$), entering three clinical trials, were assessed at baseline. Correlations, multiple linear regressions and logistic regressions tested the association between PHQ-9/GAD-7 scores and the risk factors. At baseline, 16.9% ($n = 22$) and 10.8% ($n = 14$) of patients were experiencing moderate-severe symptoms of depression and anxiety, respectively. The results of the regression indicated gender ($\beta = -0.15$, $p = 0.056$), social support ($\beta = -0.17$, $p = 0.043$), negative life events ($\beta = 0.17$, $p = 0.044$) and fatigue ($\beta = 0.58$, $p < 0.001$) explained 57% of the variance in depression scores (F (4, 78) = 25.70, $p < 0.001$). Additionally, cancer-specific stress ($\beta = 0.56$, $p < 0.001$) and social support ($\beta = -0.25$, $p = 0.006$) predicted 40% of the variance in anxiety scores (F (2, 111) = 36.14, $p < .001$). Non-ASCO risk factors are important in order to predict depressive and anxiety symptoms in patients with CLL.

Introduction

When an individual is diagnosed with cancer they are launched into a new routine that is full of doctor's appointments, aggressive medical treatments and altered life styles. These life changes can affect patients beyond their physical illness. Unfortunately, 13-40% of cancer patients experience symptoms of depression and 10-30% experience symptoms of anxiety (Bottino, Fráguas, & Gattaz, 2009; Coyne, Stefanek, & Palmer, 2007; Kissane et al., 2004; Roy-Byrne et al., 2008). Symptoms can be overwhelming to an individual and may affect many areas of their life as well as the effectiveness of treatment (Costanzo, Sood, & Lutgendorf, 2011). The National Comprehensive Cancer Network (NCCN) has recognized the impact of mental distress and has taken action to address the psychological impact of cancer (Thornton, Andersen, Crespin, & Carson, 2007).

As of 2014, NCCN guidelines require screening for anxiety and depressive symptoms in all cancer patients at Comprehensive Cancer Centers, such as the James Cancer Hospital & Solove Research Institute in Columbus, OH (NCCN, 2014). Guidelines were established to address a patient's bio-psychosocial (biological, psychological and social) needs associated with a cancer diagnosis and treatment. Psychological and social factors impact the biological effects of cancer through the immune system (Thornton et al., 2007). This emphasizes the need to focus on theses factors, in addition to patients' physical burdens. In order to construct a more comprehensive treatment that includes psychological care for cancer patients, the first step is to identify factors that place an individual at risk for anxiety and depressive symptoms.

The symptoms associated with anxiety and depression can greatly impact an individual's daily life and cancer treatment. Depression is associated with symptoms of depressed mood or irritability, decreased interest or pleasure, significant weight change (5%) or change in appetite,

change in sleep, change in activity, fatigue or loss of energy, guilt/worthlessness, concentration, and suicidality (American Psychiatric Association, 2013). Anxiety can present as chronic worry, difficulty controlling worry, restlessness, becoming easily fatigued, having difficulty concentrating, and sleep disturbance (American Psychiatric Association, 2013). Depression and anxiety are psychological disorders, but can include physical symptoms. Physical ailments associated with depression and anxiety includes muscle tension or fatigue. Depression and anxiety can also impact cancer treatment indirectly. If a patient is lacking motivation, is fatigued, and/or is having suicidal thoughts, they may not adhere to medications, appointments, and other medical treatments (Berry, Blonquist, Hong, Halpenny, & Partridge, 2015; Greer, Pirl, Park, Lynch, & Temel, 2008). Depression and anxiety are also associated with a decrease in immune system functioning in cancer patients, which can impact the trajectory of their recovery (Thornton et al., 2007).

Mental Health and the Immune System

Research has shown how the relationship between stress and the immune system can impact the course of a disease such as cancer (Andersen, Kiecolt-Glaser, & Glaser, 1994). Specifically, the bio-behavioral model developed by Dr. Barbara Andersen illustrates the relationship between a cancer diagnosis, immunity and the disease course (Figure 1). It contains two behavioral pathways (health behaviors and compliance) and two biological (central nervous system and neuroendocrine- immune) pathways that connect stress to the immune system. The behavioral and biological processes can produce specific changes in the immune system. One of the most reliable markers of this change is lowered natural killer (NK) cell activity. For example, a study looking at the affect of chronic stress on women who had recently undergone surgery for

breast cancer found that lower NK cell lysis was significantly predicted by the woman's stress level (Andersen et al., 1998).

The more stress an individual is burdened by, the greater deterioration of the immune system (Thornton et al., 2007). Chronic stress continually activates the sympathetic nervous system (Thornton & Andersen, 2006). The fight or flight response is supposed to be a short mechanism for brief threats (Dhabhar & Mcewen, 1997). However, when it is overused with chronic stressors, it adapts and leads to decreased activation of the HPA axis and decreased immune response (McEwen, 2001). A study using rats showed that chronic stress by repeated handling, restraint or crowding caused a decreased HPA response over time (Bugajski, 2003).

The etiologies of depression still remain unknown, but stress seems to have a bidirectional relationship with depression. As described above, stress has a close relationship to the immune system (Andersen et al., 1994). Symptoms of depression may be generated from peripheral inducers of immune cytokines. (Yang, Zhao, Wang, Liu, & Zhang, 2015). Cytokines affect a wide range of symptoms involved with depression, such as cognition, sleep and reward (Wong & Licinio, 2001). Depressive symptoms may also be precipitated by stress. There is consistent evidence to show there is an association between stressful life events and onset of a depressive episode and a dose-response relationship between stress and depressive symptoms (Kessler, 1997). Although the connection between depression and stress is not completely delineated, evidence does point to an association between the two psychological phenomena.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common adult form of leukemia in western countries (Kipps et al., 2017). It is characterized by an abnormal overgrowth of leukemia cells (atypical lymphocytes), which directly effects the immune system (PDQ Adult Treatment

Editorial Board, 2016). In order for blood stem cells to develop into white blood cells, they first mature into lymphoid stem cells and then lymphoblasts. Lymphoblasts then evolve into B lymphocytes, T lymphocytes and natural killer cells. CLL affects B lymphocytes. As the abnormal B lymphocytes accumulate in the blood and bone marrow, there is less room for healthy, infection fighting white blood cells. This impacts the normal functioning of the immune system, making it more difficult for the body to protect itself against infections.

CLL is a cancer that compromises the immune system. Unfortunately, mental distress has been shown to decrease immunity (Thornton et al., 2007). By further deteriorating the immune system of the patient, there are increased rates of mortality (Hamer, Chida, & Molloy, 2009). This shows the dire need to identify who is depressed and anxious. The American Society of Clinical Oncology (ASCO) has developed a list of risk factors for developing symptoms of depression. There are also other factors related to cancer patients, and specifically to those with CLL, that have been tested to determine who is more at risk for developing symptoms of anxiety and depression. Better interventions and preventive measures can be established by examining the ASCO risk factors, cancer-specific factors and CLL-specific factors.

ASCO Risk Factors

ASCO formulated a list of factors specific to cancer patients that places an individual more at risk for depression and include history of prior depressive disorder or other psychiatric disorder, family history of depression, presence of an additional chronic illness, singleton status (single, not married, widowed, divorced), unemployment/low SES and female gender (Andersen et al., 2014). Past research has supported that individuals with these factors are more at risk for developing symptoms of depression and anxiety. Kissane et al. (2004) found that past psychiatric history was positively associated with current depression diagnoses in 303 women with early and

advanced stage breast cancer. Other researchers support the association between present depressive symptoms and past psychiatric history (Grassi, Malacarne, Maestri, & Ramelli, 1997; Stafford et al., 2015)

He, Johnston, Zeitlinger, City & City (2015) examined the risks of chemotherapy toxicity in 500 older adults with a variety of cancers. Additionally, they conducted a secondary analysis on anxiety and depression. Both anxiety and depression correlated with number of comorbidities. Shreders et al. (2018) found that Patient Health Questionnaire (PHQ-9) scores equal to or above 9 (high risk for depression) was correlated with a high Charlson Comorbidity Index score.

Another study with 400 cancer patients (lung 28.6%, gastrointestinal 27.0%, gynecological 17.4%, breast 11.4%, genitourinary 10.0% and other 5.6%) being treated in a outpatient setting were assessed over the phone with a depression inventory, anxiety inventory, structured clinical interview for DSM and sociodemographic inventory (Lima, Longatto-Filho, & Osório, 2016). Their sample was 61.5% female, predominately married, and of varying education. They found that being single, not married, divorced or widowed was a risk factor for developing some type of anxiety disorder. Researchers completed a systematic review on head and neck cancer patients and also found that singleton status was associated with depression (Haisfield-Wolfe, McGuire, Soeken, Geiger-Brown, & De Forge, 2009). It was hypothesized that this is due to lack of social support.

Higher levels of depressive and anxiety symptoms have also been associated with lower socio-economic status (Simon & Wardle, 2008). A study with breast, prostate and colorectal cancer patients were assessed at 1-3 months and 10-13 months post diagnosis on socioeconomic status, medical characteristics, psychosocial wellbeing, anxiety, depression, social difficulties and benefit finding. There were more women (68%) than men (32%) due to the large sample of

breast cancer patients (58%). Composite markers separated the patients into two groups: lower SES (n = 195) and higher SES (n = 141). The lower SES patients had higher anxiety and depressive symptoms than the higher SES. This finding appeared to be more pronounced in cancer patients than a healthy control group. In the cancer population, women were more at risk for depression and anxiety (Lima et al., 2016; Lo-Fo-Wong et al., 2016; Pashos et al., 2013). Lima, Longatto-Filho & Osório (2016) found that being female was a risk factor for depression and being male was a protective factor, reducing the risk by 71%. Researchers found that women experienced more symptoms of depression and anxiety comparatively to men in a study on 1,140 patients (men= 62%, women=38%) with a hematological cancer (Pashos et al., 2013). This finding is consistent with the general population, that women experience depression two times more likely than men (Seedat et al., 2009).

Cancer-Specific Factors

Prior research has indicated that there may be additional risk factors for anxiety and depression in patients with CLL that were not included in the ASCO guidelines. These risk factors are cancer-specific stress, low social support, low number of social contacts, negative life events and younger age. Research on cancer-specific stress is minimal. However, Kang, Park & McArdle (2012) evaluated cancer-specific stress in 100 women whom had recently been diagnosed with breast cancer. The Impact of Life Events Scale (IES) was used to measure cancer-specific stress and the Profile of Mood States (POMS) to evaluate mood disturbances. They found that cancer-specific stress showed a positive association with mood disturbances. Goyal et al. (2018) recently found a relationship between cancer-specific stress and more cognitive-affective depressive symptoms in patients with CLL.

Researchers looked at social support and the well-being of 417 patients with chronic myeloid leukemia (CML) (Efficace et al., 2016). High social support was associated with lower levels of anxiety and depression [31]. Morrison, Flynn, Jones, Byrd & Andersen (2016) evaluated levels of social support in comparison to levels of anxiety and depression in patients diagnosed with chronic lymphocytic leukemia (CLL). These results supported those found by the study on patients with CML. The analysis showed that lower social support was related to and a moderator of higher levels of depressive symptoms.

The same trend was found with perceived social support and number of social contacts (Grassi et al., 1997; Sahin & Tan, 2012). Sahin and Tan (2012) looked at loneliness, depression and social support for 60 patients with a variety of cancers and 60 caregivers. There was a significant inverse relationship between social support and depression; the higher the social support, the lower the depression score. Grassi, Malacarne, Maestri & Ramelli (1997) looked at depression, psychosocial variables and occurrence of life events in 120 cancer patients. The psychosocial variables they evaluated were social support and social contacts. For analyses they divided participants based on whether they met criteria for depression or not. Those who were classified as depressed had higher scores on social contacts than those who were not depressed. Higher scores on this measure indicate lower support. This trend was also found for social support.

Grassi et al. (1997) also looked at the impact of life events on depressive symptoms. They evaluated sixty-four possible negative events in different areas such as work, education, finance, health, bereavement, family and social. Patients who met criteria for depression had more negative life events than those who did not meet criteria.

Age has been negatively associated with symptoms of anxiety and depression (Avis et al., 2012; Haisfield-Wolfe et al., 2009). Haisfield-Wolfe, McGuire, Soeken, Geiger-Brown & De Forge (2009) found that eight studies supported the association between depression and younger age in a meta-analysis on the prevalence and correlates of depression among head and neck cancer patients. The younger the individual, the more depressive and anxious symptoms they may experience.

CLL-Specific Factors

Patients with more symptoms of anxiety and depression are hypothesized to be recently diagnosed, have higher absolute lymphocyte counts and have higher levels of fatigue. These three factors are specific to a diagnosis of CLL. Absolute lymphocyte counts are used as a parameter associated with poorer outcomes in patients with CLL (Kipps et al., 2017). The higher the absolute lymphocyte count (>50,000 cells per μl), typically the worse the prognosis. Because of this correlation, absolute lymphocyte counts in combination with other risk factors may determine whether the individual needs immediate treatment for anxiety and depressive symptoms. No research has currently been completed on absolute lymphocyte counts and symptoms of depression and anxiety, but it is hypothesized that higher lymphocyte counts (worse prognosis) will be associated with more symptoms of anxiety and depression.

Morrison et al. (2016) looked at physical symptom burden and psychological response in individuals with CLL. The population contained 112 patients with a mean age of 61. They delineated the most common physical and psychological symptoms experienced by this population. The most common physical symptom expressed was fatigue. Fatigue was first measured as “tiredness” on a scale from 0 “none in the past month” to 3 “more than three times a week” and was prevalent in 57.9% of the population. It was also measured using the Fatigue

Symptom Inventory (FSI). They made a composite score of physical symptom burden, which included fatigue. The analysis showed that greater symptom burden covaried with an increase in depression and anxiety. This does not directly indicate the effect of fatigue on symptoms of depression and anxiety, but another study did evaluate its negative effects. Chang and Chen (2004) looked at 121 patients with a variety of cancers and found a connection between symptoms of depression and fatigue. For the analyses, patients were split into either depressed or not depressed categories. The patients who were categorized as depressed had a prevalence of 67% experiencing fatigue, while only 32% of the non-depressed patients experienced fatigue. Researchers found that fatigue was correlated with depression and anxiety in 716 patients diagnosed with different types of cancers (Aass, Fosså, Dahl, & Moe, 1997).

No research has looked at the differences in symptoms of anxiety and depression between patients with CLL that have been recently diagnosed compared to those who have already gone through treatment. However, Stafford et al. (2015) assessed patients with breast and gynecological cancers. The levels of anxiety (18.1%) and depression (33.3%) were highest at diagnosis. Both anxiety and depression significantly declined with time. Shanafelt et al. (2007) found that those with lower emotional quality of life were either currently in treatment or had been previously treated in patients with CLL. These are somewhat contradictory findings.

Past research on the ASCO, cancer- and CLL-specific risk factors for anxiety and depression were examined above. However, most of the studies had samples of patients with cancers other than CLL. This shows a gap in the research on anxiety and depression in patients with CLL. Pashos et al. (2013), Morrison et al. (2016), and Goyal et al. (2018) are the only studies with a sample of CLL patients that have evaluated the connection between high depressive and anxiety symptoms to the female gender, lack of social support, and cancer-

specific stress. Additional chronic illness(s), singleton status, unemployed/low SES, social contacts, age, absolute lymphocyte count, relapse refractory (R/R)/tx naïve, and fatigue have not been evaluated in a CLL population.

Goals

Aim 1: We hypothesize that those with higher levels of depressive (PHQ-9) and anxiety (GAD-7) symptoms will have a past history of a psychiatric illness, the presence of additional chronic illness(es) (Charlson Comorbidity Index), singleton status (single not married, widowed, divorced), and will be unemployed/low SES and female.

Aim 2: We hypothesize that those with higher levels of depressive (PHQ-9) and anxiety (GAD-7) symptoms will have more cancer-specific stress (Impact of Events Scale), less social contacts (Social Network Index) and support (National Institute of Health Toolbox Social Relationship Scale), more life events and will be younger.

Aim 3: We hypothesize that those with higher levels of depressive (PHQ-9) and anxiety (GAD-7) symptoms will have higher absolute lymphocyte counts, be treatment naïve, and report more fatigue (FSI).

Method

Patients

Patients (N = 130) were primarily male (43 females and 86 males), Caucasian (98%), and married (80.8%), with an average age of 60 (SD = 9.79). Ninety-three patients (71.6%) had at least some college and 114 (87.6%) made over $50,000 in yearly income (see Table 1). There were 86 people who have not been previously treated and 44 people that were relapsed or refractory patients at baseline.

Procedure

This study used baseline data collected from OSU 15012 (NCT02518555), OSU 14123 (NCT02296918), and OSU 14266 (NCT02427451). OSU 15012 is a randomized phase II trial that assesses vaccine efficacy in patients taking ibrutinib ("Ibrutinib as an Immune Modulating Agent for Patients WIth Asymptomatic, High-risk CLL/SLL Risk Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma," 2016). This trial is specifically for patients (n = 43) who have previously been untreated, are asymptomatic and have high-risk CLL.

OSU 14266 is a phase Ib/II trial attempting to determine the most effective dosage of Bcl-2 Inhibitor GDC-0199 in combination with obinutuzamab and ibrutinib ("Bcl-2 Inhibitor GDC-0199 in Combination With Obinutuzumab and Ibrutinib in Treating Patients With Relapsed, Refractory, or Previously Untreated Chronic Lymphocytic Leukemia," 2017). Patients (n = 44) were diagnosed with CLL that was relapsed/refractory (CLL has returned or has not responded to treatment) (R/R) (n = 20) or had previously not been treated (n = 24).

Finally, OSU 14123 is a trial looking at the overall response rate at 12 months for acalabrutinib (ACP-196) in combination with obinutuzumab ("Acalabruntinib in Combination With Obinutuzumab in Relapsed/Refractory or Untreated CLL/SLL/PLL," 2016). Patients (n = 43) include those diagnosed with intermediate or high risk CLL that have been previously or not previously treated. The study is split into two cohorts: the first is patients with R/R CLL (n = 19) and the second is patients who are treatment naïve (n = 24).

Patients diagnosed with CLL and enrolled in one of the three clinical trials at a Midwestern Comprehensive Cancer Center were included in this study. Trained assessors of the Stress and Immunity Cancer Projects Lab collected the data via an in-person interview format assessment. The assessments were conducted on the first day of the clinical trial.

Measures

Predictor.

a. *ASCO risk factors:* Gender, marital status, job status, income and psychiatric history were used. The Charlson Comorbidity Index (CCI) is a 19-item measure of different chronic illnesses and are scored from 1-6 based on the severity of the illness and mortality risk (Charlson, Pompei, Ales, & MacKenzie, 1987). These scores were then summed for a total score that was unadjusted for age and ranges from 0 to 35.

b. *Cancer-specific factors:*

Three measures were used. Cancer-specific stress is measured using the Impact of Events Scale (IES) (Horowitz et al., 1979). The IES is a 22-item measure that is summed with a total score ranging from 0 to 64. The higher the score, the more cancer-specific stress a patient is experiencing.

The Social Network Index (SNI) is a 16-item measure that evaluates social contacts (Berkman, 1979). The scores range from 0-12. The higher the score, the more social connection.

The National Institute of Health Adult Social Relationship Scales (NIH TB IS/ES SF) is a 21-item measure of social support ranging from 0-84 (Cyranowski et al., 2013). Five of the items are reverse scored and then the items are summed. The higher the total score, the higher the social support. The NIH TB IS/ES SF was only included in two out of the three trials.

Life Events is a 5-item measure assessing major negative stressors (e.g., death of a close friend or relative) with responses of *No/Yes* (Mundy-Bosse, Thornton, Yang, Andersen, & Carson, 2011). The items are summed for a possible score ranging from 0-5.

c. *CLL-specific factors:*

Three variables were assessed. Absolute lymphocyte counts (ALC) are used to diagnose individuals with CLL and were collected from whole blood samples the same day as the assessments (Kipps et al., 2017).

The Fatigue Symptom Inventory (FSI-R) is 11-items and measures fatigue signs and their impact on activities (Jacobsen, 2004). A 7-item subset (Total Disruption Index, TDI) was used. Items were summed for a score ranging from 0 to 70. Number of prior treatments was obtained.

Outcome Measures.

The PHQ-9 is a 9-item measure assessing for symptoms of depression (Kroenke, Spitzer, & Williams, 2001). Items are summed and total scores range from 0-27. Cut-off values for the PHQ-9 are none/mild = 1-7, moderate = 8-14, moderate to severe = 15-19 and severe = 20-27 (B. L. Andersen et al., 2014).

The GAD-7 is a 7-item measure assessing symptoms of anxiety (Spitzer, Kroenke, Williams, & Löwe, 2006). Items are summed and scores range from 0-21. Cut-off values for GAD-7 are none/mild = 0-9, moderate = 10-14, and moderate-severe, severe = 15-21 (B. L. Andersen et al., 2014).

Analytic Plan

SPSS version 24 was used for all analyses. Data from each trial was aggregated. First, descriptive statistics for gender, marital status, job status, income, life events, social contacts, social support, fatigue, age, absolute lymphocyte counts, number of prior treatments, depression, and anxiety are reported.

Second, Pearson's correlations between the GAD-7 and PHQ-9 and predictor continuous variables (CCI, Income, IES, NIH TB IS/ES SF, SNI, Life Events, Age, Absolute Lymphocyte

Counts, and Fatigue) were calculated. Point bi-serial correlations were completed for dichotomous variables (Past psychiatric history, gender, marital status, and cohort). The ASCO, cancer-specific and CLL-specific factors that were significant to $p < 0.1$ were used in multiple linear regression models.

The first model used ASCO factors to predict PHQ-9 scores. The second model had ASCO, cancer-specific and CLL-specific risk factors to predict PHQ-9 scores. The third model used backward selection to create a model with all significant factors to predict PHQ-9 scores. This was repeated for models 4-6 to predict GAD-7 scores. The model summary statistics and change in R^2 were used to show the amount of variance the factors explained in the PHQ-9 and GAD-7 models. An alpha level of 0.05 was used to identify significant predictors.

Ancillary analyses used logistic regression models to predict diagnostic levels of the PHQ-9 and GAD-7. Factors that were correlated with GAD-7 and PHQ-9 scores were used to create an ASCO model, cancer- and CLL-specific factor logistic model. Backward likelihood ratio (LR) selection was used to create final models.

Results

Descriptive statistics are provided (see Table 1). According to ASCO cutoff values, at baseline there were 83.1% ($N = 108$) with none/mild symptomology of depression, 12.3% ($N =16$) with moderate symptomology and 4.6% ($N = 6$) with moderate-severe symptomology. For the GAD-7, 88.5% ($N = 115$) of patients had none/mild symptomology, 7.7% ($N = 10$) moderate and 3.1% ($N = 4$) severe.

Correlations between the PHQ-9 and all of the risk factors showed that past psychiatric history, gender, cancer-specific stress, social support, life events, age and fatigue were all significantly correlated to at least $p < 0.1$ (Table 2). Correlations were also found with GAD-7

and past psychiatric history, gender, marital status, cancer-specific stress, social support, life events, age and fatigue to at least a $p < 0.1$ (Table 2).

Model 1 showed that the relevant ASCO risk factors significantly predicted PHQ-9 scores (F (2, 124) = 5.62, $p = 0.005$) ($R^2 = 0.083$) (Table 3). Only past psychiatric history was a significant predictor in the model ($\beta = 0.23$, $p = 0.011$) (Table 4). Model 2 showed that the ASCO factors, cancer-specific and CLL-specific risk factors also significantly predicted PHQ-9 scores (F (7, 75) = 14.94, $p = 0.000$) ($R^2 = 0.58$) (Table 3). The trending/significant factors in this model were social support ($\beta = -0.17$, $p = 0.054$), life events ($\beta = 0.17$, $p = 0.051$) and fatigue ($\beta = 0.54$, $p < 0.001$) (Table 5). Model 3 consisted of trending/significant factors from backward selection of all risk factors for the PHQ-9 (F (4, 78) = 25.70, $p < 0.001$) ($R^2 = 0.57$) (Table 3). Model 3 included gender ($\beta = -0.15$, p = 0.056), social support ($\beta = -0.17$, $p = 0.043$), life events ($\beta = 0.17$, $p = 0.044$), and fatigue ($\beta = 0.58$, $p < 0.001$) as significant predictors of the PHQ-9 (Table 6).

Model 4 showed that the relevant ASCO risk factors significantly predicted GAD-7 scores (F (3,122) = 5.44, $p = 0.002$) ($R^2 = 0.12$) (Table 3). Only past psychiatric history was a significant predictor ($\beta = 0.26$, $p = 0.004$) (Table 4). Model 5 showed that the ASCO factors, cancer-specific and CLL- specific risk factors also significantly predicted GAD-7 scores (F (8, 73) = 6.44, $p < 0.001$) ($R^2 = 0.41$) (Table 3). Only cancer-specific stress was a significant predictor in this model ($\beta = 0.51$, $p < 0.001$) (Table 5). Finally, model 6 consisted of only significant factors from backward selection of all risk factors for the GAD-7 (F (2, 79) = 26.31, $p < 0.001$) ($R^2 = 0.40$) (Table 3). Model 6 included cancer-specific stress ($\beta = 0.56$, $p < 0.001$) and social support ($\beta = -0.25$, $p = 0.006$) (Table 6).

The change in R^2 from Model 1 to model 2 was $\Delta R^2 = 0.50$. The change in R^2 from Model 4 to model 5 was $\Delta R^2 = 0.29$. The R^2 from models 2 and 3, and models 5 and 6 did not significantly change.

Ancillary Analyses

Logistic regression was run for the PHQ-9 and GAD-7 by dichotomizing the patients into either having none/mild symptoms of depression/anxiety (83.1%, 88.5%) or moderate/severe symptoms of depression/anxiety (16.9%, 10.8%), respectively. Patients with higher levels of fatigue were more likely to be in the moderate-severe PHQ-9 group (*O.R.* = 1.15, 95% *C.I.* = 1.08-1.23; $p < 0.001$) (Table 7). Patients in the moderate-severe category of the GAD-7 had more cancer-specific stress (*O.R.* = 1.086, *C.I.* = 1.016-1.160; $p = 0.015$) and less social support (*O.R.* = 0.94, *C.I.* = 0.89 – 0.99; $p = 0.026$) (Table 7).

Discussion

This study identified predictive risk factors for anxiety and depressive symptoms in patients with CLL. Patients with higher levels of depressive symptoms were female, had low social support, high levels of fatigue and more negative life events. Patients with higher levels of anxiety symptoms had more cancer-specific stress and less social support. The aforementioned risk factors supplement the ASCO risk factors for a more specific cancer population, CLL.

Aim 1 evaluated ASCO risk factors for anxiety and depression. Model 3 shows that only one ASCO risk factor, female gender, was trending toward significance as a predictor for depressive symptoms. This finding supports other literature that have shown the connection between female gender and high depressive symptom scores in cancer patients and more specifically, CLL patients (Pashos et al., 2013; Shanafelt et al., 2007). The past literature that found past psychiatric history, presence of an additional chronic illness, singleton status, and low

SES as being associated with higher levels of depressive symptoms was not supported in this study (Grassi et al., 1997; Kissane et al., 2004; Lima et al., 2016; Shreders et al., 2018; Stafford et al., 2015). The association between gender and anxiety symptoms was also not supported in this study (He et al., 2015; Simon & Wardle, 2008). This could be explained by much of the past literature not using patients with CLL or having higher rates of females.

Aim 2 evaluated cancer-specific risk factors for anxiety and depressive symptoms. Model 3 shows low social support and more negative life events were associated with higher levels of depressive symptoms. This finding supports other literature that found as social support decreased, depression scores increased in patients with CLL (Morrison et al., 2016). The association between negative life events and depressive symptoms is a novel finding in patients with CLL, but it is supported by a study that had a diverse cancer population (Grassi et al., 1997). Cancer-specific stress, social contacts and age were not predictors of depressive symptoms as seen in other literature (Efficace et al., 2016; Lima et al., 2016; Morrison et al., 2016; Seedat et al., 2009; Shreders et al., 2018).

Model 6 shows low social support and high cancer-specific stress were associated with higher levels of anxiety symptoms. This finding supports past literature that found low social support is associated with higher levels of anxiety in patients with CLL (Morrison et al., 2016). Cancer-specific stress has also been associated with more cognitive-affective depressive symptoms in patients with CLL and associated with more mood disturbances in patients with breast cancer (Goyal et al., 2018). There is no past literature looking at the association between cancer-specific stress and anxiety symptoms. This finding is novel and important for other researchers to investigate. Age was not a predictor of anxiety symptoms as seen in other literature (Lima et al., 2016; Shreders et al., 2018). The possible connection between social

contacts and life events with anxiety symptoms has not been evaluated in past literature and were also not supported by this study.

Aim 3 evaluated CLL-specific risk factors. Model 3 shows that fatigue was significantly associated with higher levels of depressive symptoms. Past literature has shown a relationship between fatigue and depression in a variety of cancer populations, but not specifically CLL (Aass et al., 1997; Chang & Chen, 2004). This finding provides information for the CLL population. Absolute lymphocyte counts was not a significant predictor for anxiety or depressive symptoms. This had not been evaluated prior to this study. Being treatment naïve has been associated with anxiety and depressive symptoms in past literature, but was not supported in this study (Aass et al., 1997). Fatigue has been associated with anxiety symptoms in past literature, but was not supported by this study (Chang & Chen, 2004; Goyal et al., 2018).

The multiple linear regression models show that there are risk factors that provide additional insight into predicting patients at high risk for anxiety and depressive symptoms beyond the ASCO guidelines. The change in R^2 from the ASCO models (1&4) to the cancer- and CLL-specific models (2&5) with the PHQ-9 ($\Delta R^2 = 0.50$) and GAD-7 ($\Delta R^2 = 0.29$) showed that the additional risk factors explained more of the variance in depressive and anxiety symptoms than the ASCO risk factors alone.

The logistic regression models applied the findings of the multiple linear regression to clinical cut-offs for PHQ-9 and GAD-7 scores making the findings more clinically relevant. By dichotomizing the PHQ-9 and GAD-7 scores into clinical cut-offs for significant anxiety and depression symptomology, the logistic regression was able to identify models that were applicable to patients with CLL. The logistic regression for the PHQ-9 only included fatigue and the GAD-7 model stayed the same as the linear regression, including social support and cancer-

specific stress. Fatigue is a very important symptom related to depression and CLL. Fatigue is a symptom of CLL, adverse side effect of certain treatments and symptom of Richter's syndrome (transformation of CLL with a negative prognosis) (Kipps et al., 2017). This shows how problematic fatigue is in patients with CLL. We showed that patients with low social support had higher levels of anxiety symptoms. It has also been found that lower social support is related to earlier cancer mortality (Pinquart, 2010). Cancer-specific stress is also crucial to patients with CLL due to its relationship with physical symptoms. Morrison et al. (2016) showed that a higher level of cancer-specific stress was related to an interaction between more disease signs/symptoms and low satisfaction.

The final logistic model is important for health-care personnel working with CLL patients. The risk factors can be used to identify those that may be in need of more mental health support. Not only is this important for their mental health, but also their physical health. The biobehavioral model explained the importance of mental health support due to its effects on ones physical health (Andersen et al., 1994). Hopefully, with additional mental health support, the deleterious effects of anxiety and depression on one's immune system can be combated. The bidirectional effects of one's physical and mental health show the need for not only mental health professionals, but also Oncologists, nurses, etc. who treat CLL to be aware of these identified risk factors.

The strengths and limitations are discussed. The sample was relatively large, including both treatment naïve and R/R patients. Even so, the number of individuals with moderate to severe symptoms of anxiety and depression at baseline was low compared to other studies with cancer samples (Bottino et al., 2009; Coyne et al., 2007; Kissane et al., 2004; Roy-Byrne et al., 2008). The lower severity of depression/anxiety symptoms could be due to the lower severity of

physical symptoms compared to other solid tumor cancers. This made it difficult to detect differences in those groups when running the logistic regression. Nonetheless, multiple linear regression models were still able to detect factors that were significantly associated with anxiety and depression.

Despite the social support measure only being included in two out of the three trials, it was still a significant predictor in the multiple linear regression model for depression and anxiety and a significant predictor for the logistic model for anxiety.

This study lacked diversity among the patient population. The patient population is mostly male, older, white and middle to upper class income. This is partially due to CLL mostly afflicting older male individuals (Cavenagh & Lister, 2003). The other demographic characteristics are also likely due to the study site; a large NCI designated Comprehensive Cancer Center. The James Cancer hospital provides clinical trial drugs that are cutting-edge and expensive. This draws in patients that have the resources to come to this facility.

Future Directions

These findings could be used in a clinical setting by a nurse, nurse practitioner, oncologist, etc. who interacts with patients with CLL often. The risk factors could be used to identify patients who may need more mental health care. Before this happens, the development of ways to assess these areas of one's life would need to occur. The measures used in this study could be a place to start, but it may be too arduous to include in a quick assessment. Ideally there would be a short measure that could briefly assess social support, cancer-specific stress, life events and fatigue. The James Cancer Hospital has already developed a brief screening measure that includes emotional concerns, physical symptoms, social/practical problems, spiritual concerns, cognitive concerns and health care decision-making/communication (Wells-Di

Gregorio et al., 2013). It would be valuable to add the found risk factors into this measure for patients with CLL.

These findings not only provide insight into CLL, but also encourage research into the risk factors associated with anxiety and depression in other types of cancer. This study showed that the risk factors for anxiety and depression in the general cancer population designated by ASCO, may not be applicable to all types of cancer due to the wide range of physical symptoms and treatment methods. Identifying these risk factors for subgroups of cancer diagnoses could bolster the quality of care provided to these individuals.

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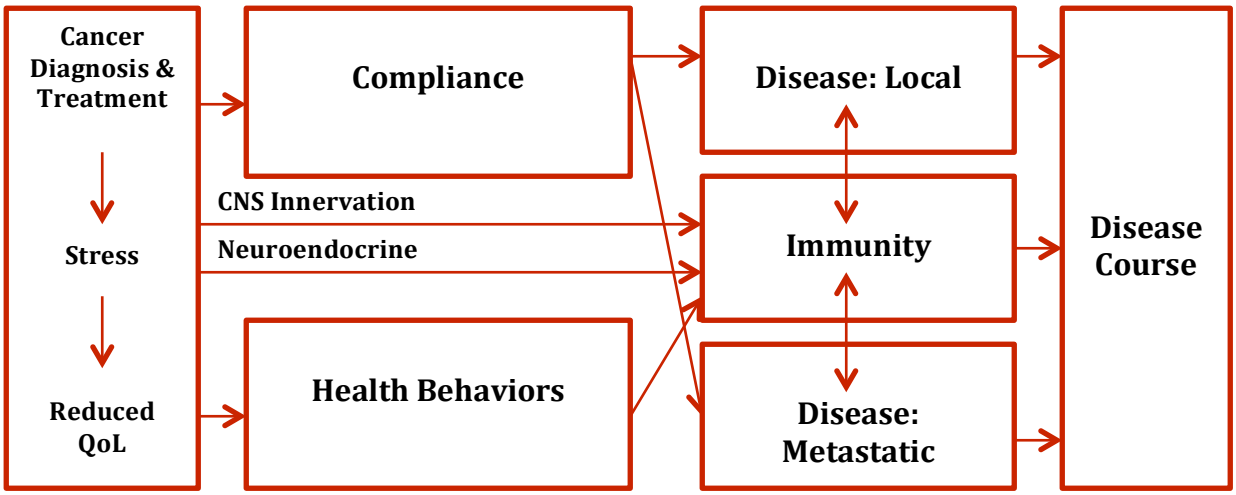

Figure 1. Bio-behavioral model showing the relationship between a cancer diagnosis, immunity and the disease course (B. Andersen et al., 1994).

Table 1

Sample Characteristics: Demographics, ASCO risk factors, Cancer-specific risk factors, CLL-specific risk factors, and outcome variables

Characteristic	Trial patients (*N*=130)	
Demographic	*M*(*SD*)	*N* (%)
Age (in years), *M* (SD)	59.63(9.79)	
Gender (Male)		86 (66.2%)
Married/Partnered (Yes)		105 (80.8%)
Race		
Caucasian		126 (96.9%)
African American		2 (1.5%)
Education		
High School/Technical School or Below		37 (28.5%)
Some College/College Graduate		56 (43.1%)
Some Graduate School/Graduate Degree		37 (28.5%)
Household income (K)		
≤ 50		16 (12.3%)
51-100		49 (37.6%)
>100		55(42.3%)
Missing		10 (7.7%)
ASCO Risk Factors		
Past Psychiatric History		20 (15.4%)
Charlson Comorbidity Index	2.76 (1.30)	
Cancer-Specific Risk Factors		
Cancer-Specific Stress	10.61 (10.36)	
Social Contacts	4.35 (2.66)	
Social Support	76.23 (11.70)	
Life Events	0.70 (0.79)	
CLL-Specific Risk Factors		
Absolute Lymphocyte Counts	83.69 (91.53)	
Treatment Naive		86 (66.2%)
Fatigue	13.05 (14.48)	
Outcome Variables		
Depression	3.88 (4.31)	
Anxiety	3.35 (4.23)	

Table 2
Correlations Between Risk Factors and PHQ-9 and GAD-7

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 PHQ-9	-														
2 GAD-7	.**67*****	_													
3 Psych His	**.25*****	**.30*****	_												
4 Charlson	.046	.026	-.12	_											
5 Gender	**-.20****	**-.21****	**-.16***	.10	_										
6 Married	-.037	**-.15***	**-.22****	.12	.069	_									
7 Income	-.056	-.030	-.017	-.10	.049	**.24*****	_								
8 IES	**.51*****	**.64*****	**.27*****	-.11	**-.29*****	-.13	-.042	_							
9 SS	**-.46*****	**-.33*****	**-.24****	.025	-.002	**.25****	**.23****	**-.19***	_						
10 SC	-.025	-.097	-.13	.12	.021	**.59*****	**.36*****	-.10	.19	_					
11 LE	**.30*****	**.17***	.13	-.022	-.039	-.13	**-.22****	.10	**-.40*****	-.13	_				
12 Age	**-.21****	**-.26*****	**-.15***	**.28*****	.10	.14	-.23**	-.36***	.051	-.079	-.041	_			
13 ALC	.053	.050	-.011	.083	**-.16***	.006	.043	-.087	.099	.081	-.025	-.015	_		
14 Cohort	-.13	-.039	.051	.11	.092	-.063	-.066	-.077	.078	**.15***	-.110	.094	**-.18****	-	
15 Fatigue	**.71*****	**.48*****	**.19****	.068	-.063	-.72	**-.17***	**.46*****	**-.37*****	-.085	**.22****	**-.077****	-.071	-.009	-

Note. *p < 0.1. **p < 0.05. *** p< 0.01.
Abbreviations: Psych His= Past Psychiatric History; Charlson = Charlson Comorbidity Index; IES= Impact of Life events/Cancer-specific Stress; SS = Social Support; SC = Social Contacts; LE = Life Events; ALC = Absolute Lymphocyte Counts; Cohort = Treatment Naïve/ R/R

Table 3

Model Summaries for Risk Factors and PHQ-9 and GAD-7

	PHQ-9 Models						GAD-7 Models					
Model	*R*	R^2	Adj. R^2	Std. Error	*F*	*p*	*R*	R^2	Adj. R^2	Std. Error	*F*	*p*
ASCO	.29	.083	.068	4.14	5.62	.005	.34	.12	.09	3.96	5.44	0.002
ASCO, Cancer, and CLL	.76	.58	.54	2.89	14.94	<.001	.64	.41	.35	3.24	6.44	<0.001
Backward selection	.75	.57	.55	2.88	25.70	<.0001	.63	.40	.39	3.15	26.31	<0.001

Table 4

Multiple Linear Regression Predicting PHQ-9 and GAD-7 Scores Based on ASCO Factors

	PHQ-9 Model					GAD-7 Model				
Predictor	*B*	*SE*	β	*t*	*p*	*B*	*SE*	β	*t*	*p*
Constant	4.32	0.68		6.33	<.001	4.41	.99		4.45	<.001
Past psychiatric history	**2.65**	**1.02**	**.23**	**2.60**	**.01**	**2.95**	**1.00**	**.26**	**2.94**	**.004**
Gender	-1.34	0.79	-.15	-1.70	.09	-1.26	0.76	-.14	-1.66	.10
Marital Status	-	-	-	-	-	-0.88	0.91	-.09	-0.97	.33

Table 5

Multiple Linear Regression Predicting PHQ-9 and GAD-7 Scores Based on Cancer- and CLL-Specific Factors

	PHQ-9 Model					GAD-7 Model				
Predictor	*B*	*SE*	β	*t*	*p*	*B*	*SE*	β	*t*	*p*
Constant	7.93	3.52		2.25	.03	6.46	4.03		1.60	.11
Past psychiatric history	0.51	0.94	.043	0.54	.59	0.06	1.09	.005	0.05	.96
Martial Status	-	-	-	-	-	0.27	1.01	.03	0.27	.79
Gender	-1.05	0.70	-.12	-1.49	.14	-0.34	0.80	-.04	-0.42	.68
Cancer-specific stress	0.03	0.04	.07	0.74	.46	**0.20**	**0.044**	**.51**	**4.54**	**<.001**
Social Support	**-0.06**	**0.03**	**-.17**	**-1.96**	**.054**	-0.71	0.04	-.20	-1.90	.06
Life events	**0.85**	**0.43**	**.17**	**1.99**	**.051**	0.37	0.50	.08	0.78	.44
Age	-0.3	0.03	-.07	-0.80	.42	-0.004	0.04	-.01	-0.11	.92
Fatigue	**0.15**	**0.03**	**.54**	**5.96**	**<.001**	0.022	0.03	.08	0.77	.45

Table 6

Multiple Linear Regression Using Backward Selection of Risk Factors to Predict PHQ-9 and GAD-7 Scores

	PHQ-9 Model					GAD-7 Model				
Predictor	*B*	*SE*	β	*t*	*p*	*B*	*SE*	β	*t*	*p*
Constant	6.812	2.63		2.59	.011	7.82	2.44		3.21	.002
Gender	-1.307	0.67	-.15	-1.94	.056	-	-	-	-	-
Life Events	0.863	0.42	.17	2.05	.044	-	-	-	-	-
Fatigue	0.164	0.023	.58	7.23	.000	-	-	-	-	-
Cancer-specific Stress	-	-	-	-	-	0.220	0.035	.56	6.33	<.001
Social Support	-0.063	0.031	-.17	-2.06	.043	-0.088	0.031	-.25	-2.84	.006

Table 7

Logistic Regression Using Backward Selection of Risk Factors to Predict PHQ-9 and GAD-7 Scores

	PQH-9			GAD-7		
Variable	*O.R.*	95% *CI*	*p*	*O.R.*	95% *CI*	*p*
Fatigue	1.15	1.08-1.23	<.001	-	-	-
Cancer-specific stress	-	-	-	1.086	1.016-1.16	.015
Social support	-	-	-	0.94	0.89-0.99	.026